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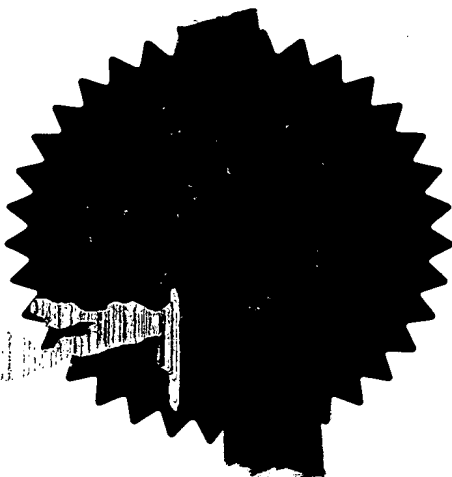
PCT

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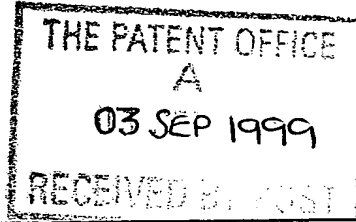
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Dated

02 OCT 2000

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)



The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

P24444/PKE/BOU

2. Patent appli

9920732.6

- 3 SEP 1999

(The Patent Office will fill in this part)

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)

Sulzer Vascutek Limited
Newmains Avenue
Inchinnan
Renfrewshire
PA4 9RR

Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

7187263001

4. Title of the invention

"Sealant"

5. Name of your agent (*if you have one*)

Murgitroyd & Company
373 Scotland Street
GLASGOW
G5 8QA

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

Patents ADP number (*if you know it*)

1198013

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (*if you know it*) the or each application number

Country

Priority application number
(*if you know it*)

Date of filing
(*day / month / year*)

-

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(*day / month / year*)

-

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer 'Yes' if:*

Yes

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or

- c) any named applicant is a corporate body.
- See note (d))

SEALANT

The present invention relates to a non-gelatine based coating or sealant for porous vascular prostheses, and to a method of making that coating or sealant.

Porous vascular prostheses constructed from textiles (such as polyester) are normally woven or knitted and ultimately rely on host tissue penetrating into the spaces between the yarns. To function in the long term the prostheses must, therefore, acquire porosity whilst at implant bleeding through the prosthesis wall must be prevented or at least limited to an acceptable level.

In the past this dilemma has been resolved by soaking a porous textile-based prosthesis in the patient's blood which then clots to form a seal. This pre-clotting technique is time consuming, exposes the prosthesis to potential contamination and may be ineffective in patients with reduced clotting ability (either reduced spontaneous blood clotting or through administration of anti-platelet or anti-thrombotic medication).

More recently, vascular prostheses have been pre-sealed

1 Dextrans of this molecular weight are freely water-
2 soluble. To form a useful graft sealant, the dextrans
3 must be rendered insoluble. However, dextrans are not
4 easily cross-linked as they have limited reactive sites
5 to form intermolecular bonds. The available groups are
6 almost exclusively hydroxyl (OH) groups.

7
8 British Patent No 854,715 describes the formation of a
9 dextran-based polymer by using epichlorohydrin.
10 However the epichlorohydrin-based approach forms very
11 stable cross-links so that the resultant polymer is
12 resistant to both enzymatic and hydrolytic attack and
13 does not biodegrade. Epichlorohydrin cross-linked
14 dextran is, therefore, unsuitable as a vascular graft
15 sealant as it is not bioresorbable and would not permit
16 tissue ingrowth within the timescale required. EP-B-
17 0,183,365 and US-A-4,747,848 both describe a gelatin-
18 based sealant in which the time-scale of reabsorption
19 is controllable.

20
21 To overcome this problem, a novel dextran-based polymer
22 has been produced which is bioresorbable through
23 hydrolysis in the time scale of interest.

24
25 The present invention provides a bioresorbable sealant
26 composition comprising a polymer formed by reaction
27 between dextran, formaldehyde and urea. Whilst the
28 dextran polymer product is insoluble, the polymer is
29 formed with bonds that are sufficiently labile to
30 permit resorption at an appropriate rate for tissue
31 ingrowth. Furthermore, when the cross-linked polymer
32 breaks down, it does so into simple products all of
33 which have a low molecular weight and which are easy
34 for the body to dispose of.

35
36 The term "dextran" as used herein includes naturally

1 between 20 to 250°C for a time sufficient to allow
2 polymerisation to occur.

3
4 The formaldehyde is conveniently added in the form of
5 formalin (a 37% aqueous solution of formaldehyde
6 hydrate). Alternatively, it would be possible to
7 bubble formaldehyde gas through the mixture of step (a)
8 to achieve the required reaction. The quantity of
9 formaldehyde required may be determined
10 stoichiometrically having regard to the amount of urea
11 added in step (a). We have found that an amount of
12 formaldehyde equivalent to 50 to 100% (by weight) with
13 reference to the amount of urea achieves the required
14 result, with 70 to 80% (by weight) being preferred.

15
16 In a further aspect, the present invention provides a
17 method of producing a non-porous graft by impregnating
18 a flexible porous material with a mixture of dextran,
19 urea and formaldehyde, and incubating said impregnated
20 material at temperatures of from 20°C to 250°C for a
21 time sufficient to facilitate cross-linking of said
22 dextran.

23
24 Preferably the temperature selected is from 30°C to
25 200°C, for example is from 45°C to 160°C.

26
27 The flexible porous material to be treated by the
28 present invention may be of any conventional type or
29 construction. Particular mention may be made of
30 polyester (e.g. DACRON™) knitted or woven fabric and
31 also of PTFE-based materials. Additionally, expanded
32 PTFE may be coated as described since, although the
33 material itself is non-porous, porosity will be
34 introduced when the graft is stitched into place by the
35 surgeon.

36

1 likely to comprise sugar units, urea, formaldehyde and
2 small complexes of the latter components. It is of
3 course possible to modify the hydroxyl groups available
4 on the dextran for reaction (see for example EP-B-
5 0,183,365).

6

7 The invention is now further described by reference to
8 the following, non-limiting, examples (together with a
9 comparative example).

10

11 **Example 1**

12

13 90 ml of water was added to 50 g of 40,000 molecular
14 weight dextran and manually mixed to encourage the
15 dextran to enter into solution. Afterwards the mixture
16 was placed on a magnetic stirrer and allowed to mix
17 continuously for 15 minutes or until the solution was
18 clear and particle free.

19

20 5 g of urea were then added to the solubilised dextran
21 and the mixture placed back on the magnetic stirrer for
22 a further 15 minutes to ensure that the urea had
23 entered into solution with the dextran. Finally, 10 ml
24 of formalin (a 38% (w/v) aqueous solution of
25 formaldehyde hydrate) providing 3.8 g of formaldehyde
26 was added to complete the mixture which was again
27 allowed to stir for 15 minutes. This mixture was the
28 impregnated into knitted polyester grafts using vacuum
29 techniques.

30

31 Gels were formed by placing the dextran impregnated
32 grafts in an oven at 150°C for 2 hours. During this
33 time a cross-linking reaction was taking place. Grafts
34 were washed for a minimum of four hours to ensure
35 removal of any residual formaldehyde. Finished grafts
36 were softened by exposure to 100% glycerol for 10

known weight in buffer and weighing the grafts again after drying to measure the amount of sealant remaining. Urea formaldehyde cross-linked dextran was found to be hydrolysed at a rate comparable to the gelatin sealant of EP-B-0,183,365.

The hydrolysis profiles of urea-formaldehyde cross-linked dextran and formaldehyde cross-linked gelatin grafts are detailed in Table 1. Hydrolysis was performed at 37°C over a period of up to 4 weeks at 125 rpm.

Table 1.

Comparative hydrolysis results for dextran and gelatin coated vascular grafts. The gelatin coated grafts were produced in accordance with Example 1 of EP-B-0,183,365.

Day	% gel degraded	
	Dextran	Gelatin*
0	0	0
3	5	30
6	15	70
12	25	95
28	95	100

*Comparative Example

Example 4 - Implantation

Grafts prepared according to Example 1 were implanted into the abdominal aorta of dogs for 2 weeks and 4 weeks respectively. Histological examination of the

